Loss of miR-203 regulates cell shape and matrix adhesion through ROBO1/Rac/FAK in response to stiffness.

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Public Summary:
Le et al. identify a signaling circuit that may protect breast epithelial cells from the tumorigenic effects of stiff extracellular matrices. Changes in the extracellular matrix can stiffen tissues and activate oncogenic signaling pathways, but cells may try to protect themselves by remodeling their cytoskeleton and cell-matrix adhesions. ROBO receptors and their extracellular SLIT ligands – best known for their role in axonal guidance – regulate Rho family GTPases and the actin cytoskeleton, and may therefore help cells sense and respond to such changes in their environment. Le et al. examined the ROBO signaling pathway in breast epithelial cells and found that ROBO1 and its ligand SLIT2 enhance cellular contractility by activating the Rac GTPase and stimulating assembly of cell-matrix adhesions. Stiffer environments caused breast cells to downregulate a microRNA, miR-203, that normally suppresses Robo1, thereby elevating ROBO1 protein levels. This, in turn, enhanced cellular contractility and adhesion, allowing cells to retain their shape and position within stiff extracellular matrices. Breast cancer cells lacking Robo1 were more invasive, suggesting that the upregulation of ROBO1 in stiff environments may prevent cells from metastasizing. Moreover, ROBO1 has previously been shown to suppress cell proliferation, suggesting that this pathway could delay tumor progression. Accordingly, breast cancer patients whose tumors displayed low miR-203/high Robo1 expression had better long-term survival rates.

Scientific Abstract:
Breast tumor progression is accompanied by changes in the surrounding extracellular matrix (ECM) that increase stiffness of the microenvironment. Mammary epithelial cells engage regulatory pathways that permit dynamic responses to mechanical cues from the ECM. Here, we identify a SLIT2/ROBO1 signaling circuit as a key regulatory mechanism by which cells sense and respond to ECM stiffness to preserve tensional homeostasis. We observed that Robo1 ablation in the developing mammary gland compromised actin stress fiber assembly and inhibited cell contractility to perturb tissue morphogenesis, whereas SLIT2 treatment stimulated Rac and increased focal adhesion kinase activity to enhance cell tension by maintaining cell shape and matrix adhesion. Further investigation revealed that a stiff ECM increased Robo1 levels by down-regulating miR-203. Consistently, patients whose tumor expressed a low miR-203/high Robo1 expression pattern exhibited a better overall survival prognosis. These studies show that cells subjected to stiffened environments up-regulate Robo1 as a protective mechanism that maintains cell shape and facilitates ECM adherence.